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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/604,400	07/17/2003	Eric T. KOOL	12665.0024.NPUS01	1399
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HOWREY LLP C/O IP DOCKETING DEPARTMENT 2941 FAIRVIEW PARK DRIVE, SUITE 200 FALLS CHURCH, VA 22042-7195			STRZELECKA, TERESA E	
			ART UNIT	PAPER NUMBER
			1637	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/604,400	Applicant(s) KOOL, ERIC T.	
	Examiner Teresa E. Strzelecka	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-49 is/are pending in the application.
- 4a) Of the above claim(s) 16-39, 42 and 43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15, 40, 41 and 44-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/17/03; 10/31/03; 9/21/04</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-16 and 40-49, species of fluorophore compound being a nucleic acid and the species of claims 41 and 44) in the reply filed on February 13, 2006 is acknowledged. The traversal is on the ground(s) that the search for all of three groups is coextensive, since, for example, the fluorophore compound of Group I contains a fluorophore and a quencher, whereas Group III encompasses nucleic acids labeled with fluorophore and a quencher. This is not found persuasive because, as can be seen in the rejections presented below, the search for the fluorophore compound does not lead to the reference for the method of Group III, which uses fluorophore and quencher-containing nucleic acids.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 16-39, 42 and 43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species and inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 13, 2006.
3. Claims 1-15, 40, 41 and 44-49 will be examined.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on July 17, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.
5. The information disclosure statement (IDS) submitted on October 31, 2003 is in compliance with the provisions of 37 CFR 1.97, except for reference C8, which does not list a place and date of

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publication. Accordingly, the information disclosure statement is being considered by the examiner with the exception of reference C8.

6. The information disclosure statement (IDS) submitted on September 21, 2004 is in compliance with the provisions of 37 CFR 1.97, except for reference C2, which is not a publication. Accordingly, the information disclosure statement is being considered by the examiner with the exception of reference C2.

Claim Interpretation

7. Applicant did not define the term "fluorophore compound", therefore it is interpreted as either unimolecular or multimolecular entity.

8. Applicant did not define the term "fluorescence quenching leaving group", therefore it is interpreted as any fluorescence quenching group.

9. Applicant did not define what it means for the fluorescence to be quenched. For example, in the case of a fluorescence donor-acceptor pair, the fluorescence intensity of the donor usually decreases in the presence of the fluorescence acceptor, therefore in this case the acceptor is considered as a fluorescence quencher.

10. Applicant did not define the terms "about 2 fold", "about 100 fold" and "about 1000 fold", therefore any value of the quenching is considered as anticipating these terms (see the rejection under 35 U.S.C. 112, second paragraph, below).

11. The art rejections presented below are based on different interpretation of the meaning of the term "fluorescence quenching leaving group", as explained above.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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13. Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-4 are indefinite over the recitation of "at least about X fold". It is vague and indefinite what is meant by the phrase "at least about 2 fold (or 10 fold or 1000 fold)". The phrase "at least" typically indicates a minimum point. The phrase "at least" however, is contraverted by the term "about" which implies that values above and below 2 (or 100 or 1000) are permitted. Further, the extent of variance permitted by "about" is unclear in this context. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the specification.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-7, 9 and 11-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Sando et al. (J. Am. Chem. Soc., vol. 124, pp. 2096-2097, February 2002; cited in the IDS).

Regarding claim 1, Sando et al. teach a 13 bp nucleic acid probe comprising fluorescein (= fluorophore) and dabsyl (= fluorescence quenching group) (Fig. 1; page 2096, fourth paragraph).

Regarding claims 2-4, Sando et al. teach the efficiency of quenching of about 100 fold, anticipating the limitations of at least about 2 fold, 100 fold or 1000 fold.

Regarding claims 5 and 6, Sando et al. teach the compound being a nucleic acid (Fig. 1; page 2096, fourth paragraph).

Regarding claim 7, Sando et al. teach single-stranded nucleic acid (Fig. 1).

Regarding claim 9, Sando et al. teach the quenching group attached to the 5' hydroxyl (page 2096, fourth paragraph).

Regarding claim 11, Sando et al. teach fluorophore located three nucleotides away from the quencher (page 2096, fourth paragraph).

Regarding claims 12 and 13, Sando et al. teach 7mer probes comprising a phosphorothioate group (= nucleophilic group) at their 3' termini (page 2096, fourth paragraph).

Regarding claim 14, Sando et al. teach fluorescein (page 2096, fourth and last paragraphs).

Regarding claim 15, Sando et al. teach dabsyl (page 2096, fourth and last paragraphs).

16. Claims 1-8, 10, 11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Livak et al. (PCR Meth. Appl., vol. 14, pp. 357-362, 1995; cited in the IDS).

Regarding claim 1, Livak et al. teach a nucleic acid probe comprising a fluorophore FAM and a quencher TAMRA (Fig. 1; page 357, second and third paragraphs; page 358, first and last paragraphs; page 360, fourth paragraph).

Regarding claims 2-4, Livak et al. teach quenching efficiency of at least 2-fold (Fig. 2).

Regarding claims 5 and 6, Livak et al. teach nucleic acid probes (Fig. 1; page 357, second and third paragraphs).

Regarding claims 7 and 8, Livak et al. teach both single-stranded and double-stranded nucleic acid probes (Fig. 1; page 357, last paragraph; page 358, first paragraph; Table 1; page 360, second paragraph).

Regarding claim 10, Livak et al. teach the quenching group attached to the internal nucleotides and to the 3'-end of the probe (Fig. 1; Fig. 2).

Regarding claim 11, Livak et al. teach the quenching group attached one nucleotide away from the fluorophore (Fig. 2, probe A1-2).

Regarding claim 14, Livak et al. teach fluorescein and TAMRA (page 357, last paragraph; page 358, first paragraph).

17. Claims 1, 5-7, 9 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Xu et al. (Nat. Biotechnol., vol. 19, pp. 148-152, February 2001).

Regarding claim 1, Xu et al. teach a fluorophore compound consisting of two nucleic acid probe pairs, where the 13 bp probe contains a FAM fluorophore and the 7 bp probe contains either a ROX acceptor (= quencher) or a HEX acceptor (= quencher) (fig. 3; page 150, paragraphs 2-5).

Regarding claims 5 and 6, Xu et al. teach nucleic acid probes (Fig. 3).

Regarding claim 7, Xu et al. teach single-stranded probes (Fig. 3).

Regarding claim 9, Xu et al. teach the quenchers attached to the 5' hydroxyl group (Fig. 3; page 151, sixth paragraph).

Regarding claims 12 and 13, Xu et al. teach the compound comprising a nucleophilic phosphorothioate group (Fig. 3; page 151, fifth paragraph).

Regarding claim 14, Xu et al. teach ROX (Fig. 3).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejections based on the Sando et al. reference

19. Claims 40, 41, 44, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sando et al. (J. Am. Chem. Soc., vol. 124, pp. 2096-2097, February 2002; cited in the IDS), Tyagi et al. (U.S. Patent No. 5,925,917) and Stratagene Catalog (page 39, 1988).

A) Regarding claim 40, Sando et al. teach a composition comprising:

a first nucleic acid probe which hybridizes to H-ras oncogene sequence, the first probe comprising a fluorophore and a quencher (page 2096, fourth paragraph; Fig. 1), and

a second nucleic acid probe comprising a nucleophilic group (page 2096, fourth paragraph; Fig. 1), where the binding of the first and second nucleic acids probes to the target causes displacement of the quenching group (page 2096, fourth and fifth paragraphs; Fig. 1).

Regarding claim 41, Sando et al. teach the quenching group attached to the 5' hydroxyl of the first probe and the nucleophilic group attached to the 3' end of the second probe (page 2096, fourth paragraph; Fig. 1).

Regarding claim 44, Sando et al. teach the quenching group attached two nucleotides away from the fluorophore (page 2096, fourth paragraph; Fig. 1).

Regarding claims 46 and 47, Sando et al. teach DNA probes (page 2096, fourth paragraph; Fig. 1).

B) Sando et al. do not teach kits comprising the probes.

C) Tyagi et al. teach kits comprising probes labeled with fluorophores and quenchers (Fig. 1-5; col.24, lines 41-65; claims 79-88).

D) Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the probes of Sando et al. into a kit format as suggested by Tyagi et al. since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

20. Claims 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sando et al. (J. Am. Chem. Soc., vol. 124, pp. 2096-2097, February 2002; cited in the IDS), Tyagi et al. (U.S. Patent No. 5,925,917) and Stratagene Catalog (page 39, 1988) as applied to claim 40 above, and further in view of Seitz et al. (Angew. Chem. Int. Ed., vol. 39, pp. 3249-3252, 2000).

A) Teachings of Sando et al., Tyagi et al. and Stratagene Catalog are presented above. They do not teach probes being RNA, 2'-O-methyl-RNA, phosphorothioate DNA, LNA or PNA.

B) Steitz teaches PNA probes labeled with fluorophore and quencher (Fig. 1; Scheme 1).

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It would have been *prima facie* obvious to use PNA probes of Steitz in the kit of Sando et al., Tyagi et al. and Stratagene Catalog. The motivation to do so, provided by Steitz, would have been that PNAs bind with very high affinity and selectivity to complementary nucleic acids (page 3249, second paragraph).

21. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
4/19/06